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Editorial Comment

Local Delivery: Let's Keep Our Eyes on the Wall*

HARVEY WOLINSKY, MD, PHD, FACC
New York, New York

Many attempts to reduce restenosis after angioplasty by systemic administration of a variety of agents have not succeeded (1). Recently, the idea of local therapy of diseased segments has gained attention (2,3). The appeal is based on the ability to achieve enormous concentrations of drugs at or near the injured segment, the possibility of reduced toxicity by local application and conservation of expensive, highly specific molecular and genetic drugs (2). In a very short time, percutaneous devices have appeared that are designated porous, microporous, double-balloon, Hydrogel coated, iontophoretic and even microinjector, with retractable needles (3–5). Drug or gene delivery can utilize liposomes, microspheres, electroporated platelets or polymer matrix slabs (2,3,6,7). Clearly, the challenge of validating a device–drug combination is more complex than that of a device alone.

With few exceptions, this outpouring of ingenuity has not been matched by systematic experimental study. Questions of infusion pressure needed and volume and toxicity of solutions delivered are a few among many variables that need to be addressed (2). Add to that the lack of clearly acceptable animal models (8) and the lack of a clearly effective agent (1,2) and it is easy to see how the situation is becoming chaotic.

Problems in experimental design. My goal is 1) to address certain problems that have already appeared, and 2) to venture a suggestion as to how the situation might be improved. Lack of a good animal model for restenosis has led some to suggest that several animal models be used to validate a device–drug combination for safety and effectiveness and that the pig coronary artery be included because of its structural similarity to the human artery (8,9). The lack of an effective agent has been frustrating but may be coming to an end. Antisense oligonucleotides of the *c*-myb and *c*-myc types have been shown to suppress cell proliferation in rat, rabbit and swine arteries, with resulting enlargement of the artery lumen compared with controls (10,11).

Perhaps the greatest concern about the present situation with its numerous devices and drugs used under a variety of conditions is that an effective agent or device will be deemed ineffective, when under "proper" use it would solve the problems of restenosis. This might occur, for example, if active drug were not delivered properly or for adequate timing and duration (12) or if the device used produced more damage than the effective agent could overcome. Even small variations in porous catheter design, such as hole size and number, can greatly influence liquid delivery (2).

Damage from local therapy. It is clear that device–drug combinations can damage the artery wall. An attempt to combine high pressure angioplasty with simultaneous local liquid infusion into arterial segments has met with disastrous perforations (13). Other studies have suggested that even when used alone to deliver fluid to normal swine arteries, one porous device caused arterial damage at 10-bars syringe pressure, less at 5 bars and virtually none at 2.5 bars (14). Others have shown no significant damage in dozens of arteries at 4 to 5 bars of pressure (11,15). Even when proliferating cell nuclear antigen (PCNA) antibodies were used to assess subtle changes in cell proliferation, no increase could be seen from infusion alone through the porous catheter (Zalewski A, personal communication, June 1994). When direct wall pressure by means of the two-balloon catheter was measured in one model for damage effects, 350 mm Hg was damaging, 150 mm Hg was not (16). I have attempted to summarize many of these seemingly conflicting results in Table 1 for one type of porous catheter (17) and one double-balloon catheter (18) for which equivalent direct wall pressures are known (17). In all cases the infusion time was <1 min, and the volume infused was <3 ml, usually 2 ml. What seems striking is that for normal arteries, acceptable pressures seem to be related to wall thickness of the muscular artery, which in turn depends on the species being studied. Thinner walls require lower infusion pressures. (All arterial wall thicknesses [19,20] have been corrected for distention to physiologic pressure and for tissue shrinkage due to processing [21]). It is interesting, for example, that if only 2 bars of syringe infusion pressure is used for the *dog* peripheral artery, marker dye penetrates only one-third through the medial thickness (22), whereas 4 bars penetrates the entire wall. Similarly, if pore size is reduced to minimize pressure effects, instead of full-thickness penetration, only 15% of the wall area is stained (23). Seemingly disparate results can be made consistent when variables are controlled, as shown in Table 1.

Large molecules and the normal artery. Nowhere has the concern about possible damage been greater than among those attempting to deliver viral vectors, gene products or liposomes to the arterial wall (2,16). Cellular damage produced by device-infusion perturbations can blur demonstration of genetic or molecular effects of the infusate. Indeed, efficiency of gene manipulation has been very low when calculated on the basis of percent of medial cells showing the desired gene effect (2).

"Anatomic barriers" in the normal vessel wall have been incriminated in the limited entrance of liposomes or viral vectors at nondamaging pressures (100 to 400 mm Hg direct

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From the Division of Cardiology, Mount Sinai Hospital and Medical Center, New York, New York.

Address for correspondence: Dr. Harvey Wolinsky, Mount Sinai School of Medicine, Box 1014, One Gustave Levy Place, New York, New York 10129.

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Table 1. Relation of Wall Penetration to Wall Pressure in Muscular Arteries of Different Species

Wall Pressure* (mm Hg)	Applied Pressure† (bars)	Wall Thickness		Coronary or Peripheral Vessels
		Distended (μm)	Undistended (μm)	
50	2	50–125	75–200	Rat and rabbit
150	3	125–200	200–300	Pig
300	4	200–400	300–600	Dog and human
500	5	>400	>600	Diseased human?

*Porous balloon catheter (17). †Double-balloon catheter (18).

pressure). At higher pressures (500 mm Hg direct pressure or 5-bar syringe pressure), penetration is seen, but wall damage is considerable (24). These anatomic barriers most likely consist of the internal elastic lamina and other fibroelastic structures, which are known to impede transmural passage of circulating large molecules through normal arteries (25).

Treatment of diseased arteries. Are concerns about subtle wall damage to and anatomic barriers of normal arteries relevant to the clinical goals of local therapy? Let us remember what the clinical situation is. Angioplasty results in enormous damage to the arterial wall: tears and dissections extend through the media and adventitia (1). Hemorrhage and necrosis are seen. Other vascular diseases, such as vasculitis or atherosclerosis, which might be the object of genetic therapy, characterically destroy wall integrity, effacing the usual tight organization of normal vascular tissue.

The intimal atherosclerotic plaque subjected to angioplasty is often hundreds of microns thick, often thicker than the underlying media (19). Indeed, it has been shown that even without tears and dissections, plaque tissue is more permeable to circulating materials than the normal arterial wall (26).

Does local therapy add to damage? A fundamental question that relates to the safety and efficacy of a device-infusion system is, Does it increase the damage or wall response, or both, beyond that caused by the initial simple angioplasty or disease process? If it does not, we can then examine a drug being tested for eventual benefit on the repair process in the artery wall. In all cases, the arterial wall is the point of focus for safety and effectiveness.

In the report by Plante et al. (27) in this issue of the Journal, infusion of fluid through a porous catheter before angioplasty of rabbit iliac artery was compared with angioplasty alone. Fluid infusion caused no further stimulation of thymidine incorporation at 4 days or development of neointima at 30 days after injury compared with angioplasty alone. This reassuring finding of no added cell proliferation from infusion *and* angioplasty compared with standard angioplasty alone has also been found in the rabbit hyperplastic iliac artery model (Rosenberg R, personal communication, June 1994).

It would seem worthwhile, when viral vectors and gene-bearing liposomes are infused to alter cellular behavior, to use diseased animal models that allow ready penetration of these large carriers, a situation more akin to clinical circumstances. Previous disruption of plaque architecture (and "barriers") by mechanical means, simple induction of intimal plaques or production of medial diseases before introduction of the modifying agent seems a more appropriate test of eventual safety and efficacy under clinical conditions.

Unanswered questions. There is much that we do not know. It may not be necessary to penetrate the entire wall thickness; conversely, it would seem undesirable to force fluid beyond the adventitia and into the myocardium or other surrounding tissue. If the goal were to influence surface events, such as platelet adherence or thrombosis (28), relatively shallow deposition of active agent in the artery wall may be sufficient. However, if a sizeable depot of active drug were desired to mimic adventitial release over a longer period (7), full penetration of the entire wall might be needed.

Conclusions. I have attempted to emphasize the importance of tailoring drug–device conditions to the vascular tissue being manipulated. Artery size, thickness, disease state and previous manipulation will all affect the performance of a given technique of local delivery.

By systematic attention to these factors, more coherent interpretation of improvement or deterioration of the underlying vascular disease may be possible. Seemingly conflicting results can be accommodated in a unifying concept if these details are considered beforehand. A device or other specific local therapy can initially be assessed for general procedural details under idealized conditions using normal vessels. However, safety and utility will ultimately best be considered in models that more closely simulate the disease being treated, including previous tissue manipulation where that is part of the clinical sequence. In this way, potential harm from the intervention will neither be exagerrated nor underestimated. We can thereby increase the likelihood that experimental success will ultimately be reflected in clinical success. With so many new devices at an early stage of development, and with so many potential therapeutic agents, we can best assess the ultimate value of local therapy if we "keep our eyes on the wall."

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